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Adrenergic G protein-coupled receptors in liver physiology and pathology: research advances and clinical implications

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The liver, key for metabolism and homeostasis, sees growing focus on adrenergic GPCRs (α1/α2, β1/β2/β3; activated by adrenaline/noradrenaline). These receptors affect liver physiology/pathology and are treatment targets. This review explores their roles/mechanisms in liver diseases to aid research, clinic, and precise care.

Global burden of liver function and liver disease

The liver is a highly heterogeneous and structurally distinct organ that maintains systemic homeostasis through blood detoxification, bile acid production, and various metabolic functions[1]. Liver diseases are a leading cause of death worldwide. According to the 2019 Global Burden of Disease report, 1.26 million people died from cirrhosis and other chronic liver diseases in 2019, reflecting a 13% increase since 1990[2]. Furthermore, approximately 830,000 people died from liver cancer in 2020, accounting for 8.3% of global cancer-related deaths[3].

The role and research significance of adrenergic receptors in the liver

Multiple adrenergic receptors are present in the liver, where they play essential roles in both physiological and pathological processes, including the regulation of metabolism, inflammation, fibrosis, liver regeneration, and tumorigenesis[4]. Adrenergic receptors, a class of G protein-coupled receptors activated by adrenaline and noradrenaline, are classified into α-type (α1 and α2) and β-type (β1, β2, and β3)[5]. Therefore, a more in-depth investigation of adrenergic receptor mechanisms in the liver will not only enhance our understanding of liver function regulation in both health and disease but also open new avenues for research and provide potential intervention targets for the prevention, diagnosis, and treatment of liver diseases.

Literature search strategy for this review

Literature for this review was identified through searches of PubMed and Web of Science using the terms "adrenergic receptors," "liver diseases," "α-AR," "β-AR," "liver fibrosis," "hepatocellular carcinoma," "cholangiocarcinoma," and "MASLD," alone or in combination. The search strategy focused on original research articles, reviews, and clinical studies published primarily within the last two decades, though seminal older works were included. While this approach was less systematic than a formal systematic review, it aimed to comprehensively cover key advances. Selected evidence was critically analyzed and integrated with the our expertise in hepatology and pharmacology to provide a balanced perspective on the field.

Adrenergic receptor subtypes and their functions

α-adrenergic receptors

Subtypes, gene localization, and function of α1-adrenergic receptors (α 1-AR). α-Adrenergic receptors are classified into two main subtypes α1 and α2[6]. The α1-AR subtype is further subdivided into three subtypes α1A, α1B, and α1D, encoded by genes located on chromosomes 8p21.2, 5q33.3, and 20p13, respectively. α1 receptors primarily induce vasoconstriction, leading to an increase in blood pressure, and play a critical role in hemodynamics[7].

Subtypes, gene localization, and function of α 2-adrenergic receptors (α 2-AR). The α2-AR subtype is also divided into three subtypes α2A, α2B, and α2C, encoded by genes on chromosomes 10q25.2, 2p13.1, and 4p16.1, respectively[7]. α2 receptors are predominantly located on nerve terminals, where their activation inhibits the release of noradrenaline, thereby reducing sympathetic nerve activity[8].

β-adrenergic receptors

Gene localization, expression site, and function of β 1-adrenergic receptor (β 1-AR). β-Adrenergic receptors are classified into three subtypes β1, β2, and β3[6]. The gene encoding β1-AR is located on chromosome 10q25.3, and β1-AR is primarily expressed in the myocardium. It enhances myocardial contractility and heart rate by elevating cAMP levels[9].

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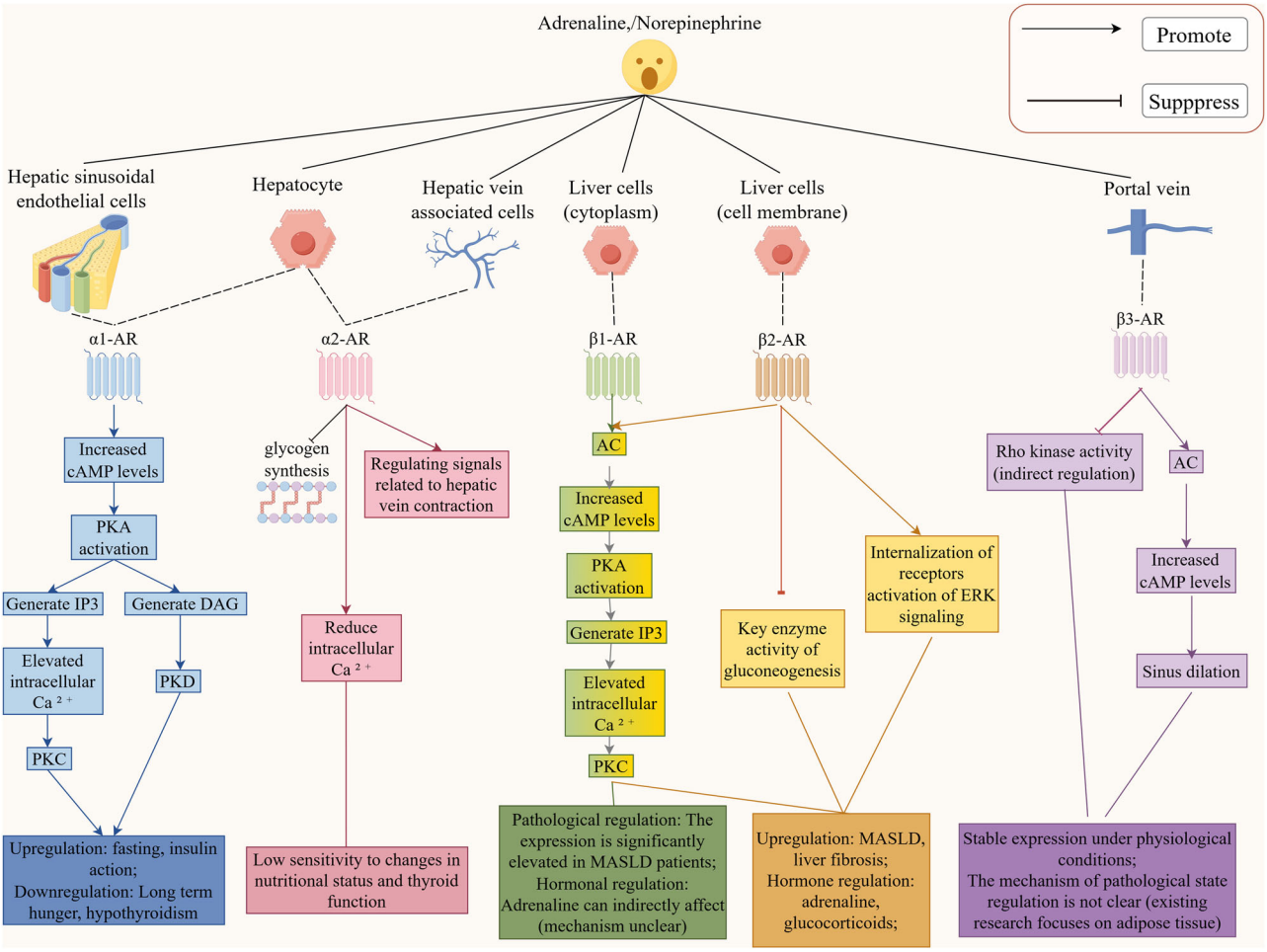

Fig. 1 | Adrenergic receptor distribution, expression regulation, downstream signaling pathways, and physiological roles in the liver (By Figdraw.). This figure illustrates the distribution of different adrenergic receptors (α1-AR, α2-AR, β1-AR, β2-AR, β3-AR) in various liver cell types and structures (hepatic sinusoidal endothelial cells, hepatocytes, hepatic vein associated cells, liver cells' cytoplasm and cell membrane, portal vein). It also shows the receptors' downstream signaling pathways (such as cyclic Adenosine Monophosphate (cAMP) - dependent and Ca^{2+} - mediated cascades), expression regulation under physiological and pathological conditions, and physiological roles. For α1-AR in hepatic sinusoidal endothelial cells, binding leads to increased cAMP levels, activating PKA, which generates IP3 and Diacylglycerol (DAG). IP3 elevates intracellular Ca^{2+}, activating PKC, while DAG activates PKD. α1-AR expression is upregulated by fasting and insulin action, and downregulated by long - term hunger and hypothyroidism. α2-AR in hepatocytes is involved in glycogen synthesis, reduces intracellular Ca^{2+}, and regulates signals related to hepatic vein contraction, with low sensitivity to changes in nutritional status and thyroid function. β1-AR and β2-AR in liver cells (cytoplasm and cell membrane) act via AC to increase cAMP levels, activating PKA. This leads to IP3 generation, elevated intracellular Ca^{2+}, PKC activation, and for β2-AR, also promotes receptor internalization and ERK signaling activation, and enhances key enzyme activity of gluconeogenesis. β receptor expression is elevated in patients with MASLD and liver fibrosis, and is regulated by hormones like adrenaline and glucocorticoids. β3-AR in the portal vein indirectly regulates Rho kinase activity via AC, increasing cAMP levels and causing sinus dilation. It has stable expression under physiological conditions, and the mechanism of its pathological regulation is unclear (current research focuses on adipose tissue). Arrows indicate promotion, and blocked lines indicate suppression.

Gene localization, expression site, and function of β 2-adrenergic receptor (β 2-AR). The gene encoding β2-AR is located on chromosome 5q31-q32, with β2-AR predominantly expressed in the smooth muscles of the lungs and airway epithelial cells[9]. Upon activation, β2-AR induces bronchial smooth muscle relaxation, improves pulmonary ventilation, and reduces inflammation and allergic reactions[10].

Gene localization, expression site, and function of β 3-adrenergic receptor (β 3-AR). The gene encoding β3-AR is located on chromosome 8p11.23, and β3-AR is mainly found in adipose tissue, where it promotes fatty acid oxidation, and energy metabolism[11–13].

Adrenoceptor distribution, expression regulation, and physiological roles in the liver

To intuitively present the distribution, regulatory factors, downstream signaling, and physiological roles of adrenergic receptors in the liver under steady-state conditions, the core characteristics of α1-AR, α2-AR, β1-AR, β2-AR, and β3-AR are visualized in the Fig. 1.

α-adrenergic receptor distribution, expression regulation, and physiological roles in the liver

Distribution of α-AR in the liver. α-Adrenergic receptors (α-ARs) are key regulators of hepatic physiological processes[14]. In the liver, intrahepatic sympathetic nerves predominantly course along the portal triads, forming dense periportal and perisinusoidal plexuses that extend toward centrilobular regions[15,16]. These nerves release norepinephrine (NE), which activates α1-ARs broadly expressed on hepatocytes and hepatic sinusoidal endothelial cells, regulating gluconeogenesis, glycogenolysis, and lipid metabolism[17–21]. α1-AR density is highest in periportal zones, aligning with sympathetic innervation patterns and facilitating zone-specific metabolic responses such as glycogen breakdown and glucose output[22,23]. In contrast, α2-AR is less

abundant and primarily localized to hepatocytes, where it modulates oxidative stress responses[20].

Expression regulation of α-ARs. The expression and function of α-ARs in the liver are tightly regulated by various physiological and pathological conditions. For instance, under fasting or insulin-treated states, α1-AR mRNA levels are upregulated, whereas during prolonged starvation or hypothyroidism, α1-AR mRNA levels are downregulated. In contrast, α2-AR expression appears more stable and less sensitive to alterations in nutritional status and thyroid function[24]. Regulation of α-ARs occurs at both transcriptional and post-transcriptional levels. Transcription factors such as CREB and NF-κB have been shown to regulate α1-AR gene expression[25]. Moreover, post-transcriptional mechanisms, including alternative splicing and RNA editing, contribute to the generation of diverse α-AR mRNA isoforms and modulate their functional responses.

Physiological role of α-AR in the liver

Regulatory effect on hepatic glycogen metabolism. The physiological role of α-ARs in the liver is primarily through regulating hepatic glycogen metabolism. The main mechanism by which the α1-AR regulates glycogen metabolism is through the activation of glycogen phosphorylase, which promotes glycogenolysis. Studies have demonstrated that selective α1-AR agonists, such as phenylephrine, can dose-dependently increase glycogen phosphorylase activity in liver homogenates and isolated hepatocytes, thereby enhancing glycogen breakdown and glucose release. This effect is independent of cAMP levels and is mediated by the binding of α1-AR, followed by phosphorylase activation. The increase in intracellular Ca2+ concentration induced by α1-AR agonists enhances the interaction between phosphorylase and phosphorylase-β kinase, thus promoting the activation of phosphorylase[26]. Additionally, α1-AR agonists inhibit the activity of phosphorylase phosphatase, further stabilizing the function of phosphorylase[27].

The role of the α2-AR in the liver is primarily to regulate glycogen synthesis by inhibiting the activity of hepatic glycogen synthase. Studies have shown that α2-AR activation significantly inhibits glycogen synthase activity, thereby suppressing glycogen synthesis. This effect may be mediated by a decrease in intracellular Ca2+ concentration induced by α2-AR activation, as Ca2+ is known to activate glycogen synthase[28].

Regulatory effect on liver blood flow and hepatic vein contraction. The role of α2-ARs in the liver is also closely associated with the contraction response of the hepatic veins. Studies suggest that norepinephrine regulates hepatic blood volume through the activation of α2-ARs, indicating that α2-ARs play a critical role in the regulation of hepatic blood flow and hepatic vein contraction[29].

Effects on liver bile flow. α-Adrenergic signaling modulates bile flow through effects on bile canalicular contraction and vascular tone. Norepinephrine activation of α1-ARs increases intracellular Ca^{2+} in hepatocytes, promoting bile canalicular contraction and influencing bile flow dynamics[30]. However, excessive α-adrenergic stimulation may induce cholestasis by increasing intrahepatic vascular resistance and impairing biliary excretion[31].

β-adrenergic receptor distribution, expression regulation, and physiological role in the liver

Distribution of β-AR in the liver. β-Adrenergic receptors (β-ARs) are a major class of adrenergic receptors, consisting of three subtypes β1-AR, β2-AR, and β3-AR. In the human liver, β2-AR is the predominant subtype, while β1-AR is relatively less abundant. Under normal conditions, β1-AR is primarily located in the cytoplasm of hepatocytes, whereas β2-AR is predominantly expressed on the cell membrane of hepatocytes[32]. The distribution of β2-AR in the liver is primarily concentrated on the surface of hepatocytes, particularly in regions associated with bile acid secretion and glucose metabolism. This distribution is closely linked to its physiological functions, especially in the regulation of hepatic glycogen synthesis and breakdown, as well as lipid metabolism[33].

β3-AR in the liver is primarily localized in the portal vein, with concentrations notably higher in the perivascular regions[34]. Although β3-AR is also present in brown adipose tissue, brown adipose tissue is not typically found in the liver[13,35]. Recent studies have suggested that small amounts of brown adipose tissue may exist in certain regions surrounding the liver, particularly in specific animal models[36]. These findings provide new insights into the potential role of brown adipose tissue in liver function.

Regulation of β-AR expression. The expression of β-ARs in the liver is regulated by various physiological and pathological factors. Studies have shown that hepatic β-AR expression is closely associated with the onset and progression of several liver diseases. For example, in patients with Metabolic dysfunction-associated steatotic liver disease (MASLD), the expression levels of both β1-AR and β2-AR are significantly elevated[37,38]. During liver fibrosis, the β2-AR expression also increases markedly.

In addition, β2-AR expression is modulated by hormones such as adrenaline and glucocorticoids. The regulatory mechanisms of β2-AR primarily involve two signaling pathways, the G protein-mediated pathway and the β-arrestin-mediated pathway. In the G protein-mediated pathway, β2-AR binds to G proteins, leading to the activation of downstream effectors such as adenylate cyclase (AC), which increases intracellular cAMP levels and activates cAMP-dependent protein kinase A. In contrast, the β-arrestin-mediated pathway involves the recruitment of β-arrestin to activated β2-AR, promoting receptor internalization and activation of downstream signaling cascades, including extracellular signal-regulated kinase (ERK) activation and nuclear translocation[39,40].

Physiological role of β-AR in the liver

Regulation of hepatic glucose metabolism and lipid metabolism. Regulating glucose and lipid metabolism is a crucial physiological function of β-ARs in the liver. β-ARs modulate glucose metabolism by inhibiting insulin secretion and increasing hepatic glucose output by stimulating gluconeogenesis and glycogenolysis[41,42]. Insulin is a key hormone involved in blood glucose regulation, facilitating glucose uptake and utilization in muscles and adipose tissue[43,44]. Studies have shown that the activation of β-AR can reduce the tyrosine phosphorylation of insulin receptor substrate, impede insulin signaling transduction, decrease insulin sensitivity, and ultimately lead to an increase in blood glucose levels[41,45].

β2-AR also regulates glucose metabolism by inhibiting the liver's endogenous glucose production. The liver is a central organ in blood glucose regulation, capable of producing glucose through gluconeogenesis to maintain glucose homeostasis. Activation of β2-AR inhibits the activity of key gluconeogenic enzymes and reduces the production of gluconeogenic substrates such as pyruvate and lactate, thereby decreasing endogenous glucose production and aiding in the maintenance of blood glucose balance. Additionally, a novel pathway has been identified in which β2-AR activation mediates glucose uptake in skeletal muscles to further regulate glucose metabolism[46]. Animal studies have shown that activation of this pathway significantly enhances glucose uptake in skeletal muscles in mice[47].

Regulatory effect on liver bile duct structure and repair. β-Adrenergic receptors regulate bile duct architecture during injury. β-AR agonists like isoproterenol enhance ductular expansion and cholangiocyte proliferation via cAMP-dependent pathways during chronic liver injury, facilitating biliary adaptation[48]. This process involves synergistic interactions with periportal mesenchymal cells, where β-AR activation upregulates fibrogenic mediators such as fibroblast growth factor 7 (FGF7), promoting bile duct remodeling and functional recovery[48].

Neuroanatomical basis for receptor zonation

The zonated expression of adrenergic receptors mirrors intrahepatic nerve distribution. Sympathetic fibers along portal triads preferentially innervate periportal hepatocytes, driving α1-AR-mediated glycogenolysis and β2-AR-mediated gluconeogenesis. Perisinusoidal plexuses in centrilobular areas express abundant β3-AR, where norepinephrine from sympathetic

terminals induces sinusoidal relaxation via cAMP-dependent pathways, reducing intrahepatic resistance[49,50]. This anatomical arrangement ensures metabolic priority in oxygen-rich periportal zones and hemodynamic regulation in perivenous regions, highlighting how neural architecture underpins the compartmentalization of adrenergic functions[22,51].

Adrenergic receptors in liver diseases

Adrenergic receptors play a crucial role in various pathological conditions of the liver, including liver inflammation, injury, steatotic liver, liver regeneration, liver fibrosis, and liver cancer[4]. The activation or inhibition of α-AR and β-AR significantly impacts the progression, development, and treatment strategies for these diseases. Therefore, studying the mechanisms of adrenergic receptors not only aids in understanding the onset and progression of liver diseases but also provides a theoretical foundation for related therapeutic approaches.

Liver inflammation

Regulatory mechanism of α 1-AR on liver inflammation (signaling pathway level). The α1-AR stimulates phospholipase C (PLC) activity through coupling with G proteins, promoting the hydrolysis of phosphatidylinositol and generating inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 triggers the release of calcium ions, which activate protein kinase C (PKC), leading to the release of inflammatory factors. DAG activates protein kinase D (PKD), further amplifying the inflammatory response. Thus, α1-AR enhances liver inflammation through the PLC-IP3/DAG-PKC/PKD signaling pathway[52,53].

Effects of β-AR on liver inflammation (cell experiments and clinical implications). β-AR also plays a significant role in liver inflammation. An in vitro study using human hepatocytes showed that catecholamines, such as adrenaline and noradrenaline, mimic the action of lipopolysaccharide (LPS), with activated β-AR leading to excessive secretion of interleukin-6 (IL-6), thereby exacerbating inflammation and inhibiting CYP3A4 expression. In contrast, vasopressin did not induce inflammation or alter CYP3A4 expression. This suggests that β-AR activation may influence hepatic drug metabolism, highlighting the need for caution in the use of catecholamine drugs in sepsis treatment[54].

In another animal experiment, treatment with novel β2 and β3-AR agonists, such as ATR-127, resulted in a reduction in liver weight and a decrease in the expression of inflammation-related genes, such as MCP1 and F4/80[55].

Liver injury

Liver protective effect of α 2-AR (mechanism using DEX as an example). Hepatocellular injury is driven by reactive oxygen species, pro-fibrotic mediators, hepatic stellate cell (HSC) activation, and myofibroblast effects, leading to tissue inflammation and disease progression[56]. A study investigating the protective effects of dexmedetomidine (DEX) against LPS-induced liver injury in rats found that DEX improved pathological damage and functional indicators of liver tissue, enhanced antioxidant activity, and reduced oxidative stress levels. Additionally, DEX modulated the expression of anti-apoptotic proteins and inhibited the upregulation of pro-apoptotic proteins in LPS-induced liver injury. The study suggests that DEX may protect the liver from oxidative stress and cell apoptosis by activating the α2-AR and regulating the GSK-3β/MKP-1/Nrf2 pathway[57]. These findings provide mechanistic insights into the protective role of DEX in septic liver injury and offer potential therapeutic strategies for the prevention and treatment of septic liver injury.

The exacerbating effect of β-AR on liver injury (drug-induced injury case). A study on methylphenidate induced hepatotoxicity in mice showed that the β-adrenergic agonist isoproterenol significantly exacerbates liver injury, increasing the liver's toxicity threshold by approximately 5–10 times. After administration of pirimicarb, serum and liver levels of pirimicarb were significantly elevated, with its area under the curve in both the liver and serum showing a significant increase. This indicates that β2-adrenergic receptor stimulation enhances the hepatotoxicity of pirimicarb, likely by increasing its concentration in the liver and intensifying toxic responses[58]. Furthermore, when administered in high doses or in cases of intentional overdose, β-adrenergic agonists can cause liver injury. This liver damage typically occurs within a few days of starting high-dose intravenous β-adrenergic agonists, is usually asymptomatic, unrelated to jaundice, and rapidly reversible upon cessation of the drug[59].

Steatotic liver (ALD, MASLD)

Adrenergic receptors play a significant role in the pathogenesis of Alcoholic liver disease (ALD) and MASLD by regulating lipid metabolism, insulin resistance, and the progression of liver fibrosis, making them potential therapeutic targets. Figure 2 illustrates the roles of adrenergic receptors in the progression from a healthy liver to ALD and MASLD, highlighting their involvement in fat deposition, fibrosis, and energy metabolism.

Role in alcoholic liver disease (ALD) (association of receptors with adipogenesis and fibrosis). One of the major consequences of alcohol consumption is ALD, which is characterized by excessive accumulation of triglycerides and cholesterol in hepatocytes[60]. An animal study demonstrated that ethanol metabolism-induced lipogenesis might trigger a feedback loop of HSC activation via sympathetic nervous system (SNS) activation, leading to excessive production of TNF-α (a mediator of fat production) from activated HSCs. The adrenergic receptors (α1, β1, and β2) in ALD promote lipogenesis and liver fibrosis progression through SNS activation. Inhibition of these receptors, such as using carvedilol, effectively reduces liver fat accumulation and fibrosis, providing a new strategy for treating ALD[61].

Role in metabolism related fatty liver disease (MASLD)

Association with insulin resistance (IR). MASLD is a liver condition associated with obesity, diabetes and metabolic syndrome, characterized by over 5% of hepatocytes showing hepatic steatosis with little or no alcohol consumption[62,63]. MASLD is closely linked to insulin resistance (IR) and type 2 diabetes, with IR playing a crucial role in the pathogenesis of MASLD and in the progression from steatosis to non-alcoholic steatohepatitis[64,65]. An animal experimental study showed that activation of α2-AR can alleviate IR induced by a high-fat diet (HFD) in MASLD mice, suggesting that adrenergic receptors play a critical role in the pathogenesis of MASLD[66].

Regulation of β 2-AR on fat deposition (mechanisms of lipid synthesis and oxidation). Obesity and ageing activate the sympathetic nervous system, enhancing β2-AR signaling in the liver, which may promote the development of MASLD. β2-AR agonists can induce hepatic steatosis in mice, significantly increasing hepatic triglyceride levels and lipid droplet accumulation. This effect may be related to β2-AR activation, which promotes hepatic lipid synthesis and de novo lipogenesis. β2-AR agonists can significantly increase the expression of lipid synthesis-related genes (such as SREBP-1c, FAS, and DGAT1) and the expression of lipid droplet-associated proteins (such as Cidea, Cideb, and Plin), thus exacerbating hepatic fat accumulation. Furthermore, β2-AR agonists can enhance the expression of PPARα and PGC-1α, promoting fatty acid β-oxidation. However, incomplete β-oxidation leads to the accumulation of long-chain acylcarnitines, which may be linked to mitochondrial dysfunction, further intensifying hepatic fat deposition[37].

The role of β 3-AR and the impact of gene polymorphism. Additionally, β3-AR also plays a role in lipid metabolism, indicating that adrenergic receptor activation is important in the development of MASLD. Activation of β3-AR promotes fatty acid oxidation and energy metabolism, regulating energy balance. This may exacerbate the course of MASLD by inhibiting lipolysis and increasing visceral fat deposition.The Trp64Arg polymorphism

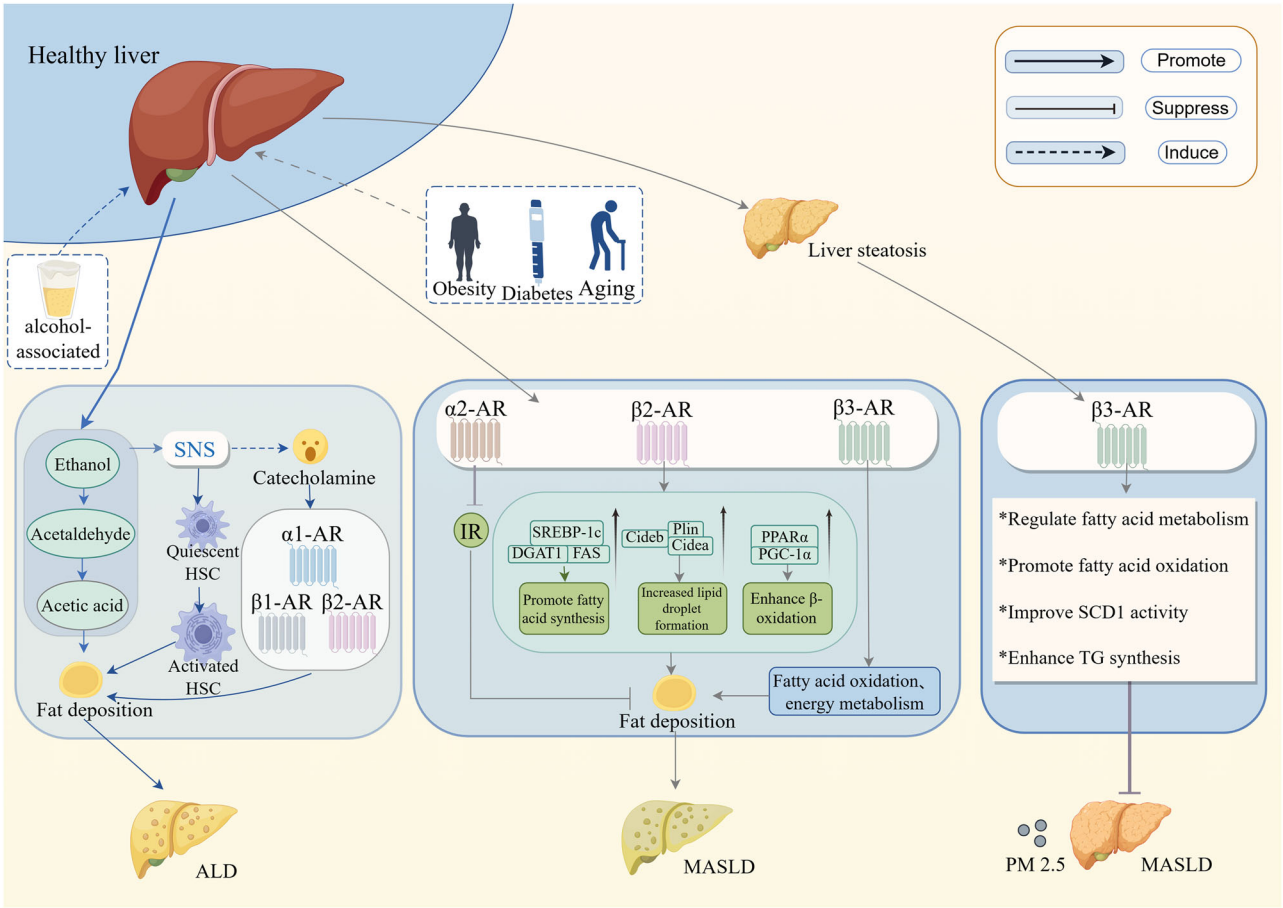

Fig. 2 | Roles of adrenergic receptors in the progression from healthy liver to ALD and MASLD (By Figdraw.). This figure depicts the progression from a healthy liver to ALD and MASLD, emphasizing the distinct roles of α1-AR, α2-AR, β1-AR, β2-AR, and β3-AR in these conditions. In the ALD pathway, ethanol is metabolized into acetaldehyde and then acetic acid, promoting fat deposition. This process, along with the activation of α1-AR, β1-AR, and β2-AR within the SNS, drives liver fibrosis and ALD development. For MASLD, insulin resistance triggers the α2-AR pathway, which upregulates factors like Sterol Regulatory Element - Binding Protein - 1c (SREBP - 1c) to promote lipid synthesis and lipid droplet formation, causing hepatic fat accumulation. While β2-AR activation facilitates fatty acid β - oxidation, mitochondrial dysfunction can counteract this, still leading to fat accumulation. β3-AR regulates fatty acid oxidation and energy metabolism in MASLD; however, it may also exacerbate the condition by inhibiting lipolysis and promoting visceral fat accumulation. Notably, β3-AR activation can improve lipid metabolism disorders and alleviate MASLD induced by PM2.5 (Particulate Matter ≤2.5 μm) exposure, showcasing its dual - faced role.

(rs4994) within the β3-adrenergic receptor (β3-AR) gene has been implicated in an elevated susceptibility to MASLD in small-scale observational studies. Individuals harboring the C allele of this polymorphism exhibit a higher propensity for metabolic disturbances, including obesity and insulin resistance. Nevertheless, the direct causal link between this genetic variant and MASLD progression, as well as its translational potential in clinical practice, necessitates further validation through large-sample, multi-center prospective cohort studies[67].

Improvement effect on MASLD (PM2.5 induced injury case). The diagnostic criteria for MASLD are based on hepatic steatosis and require metabolic dysregulation factors as prerequisites, primarily including type 2 diabetes, overweight/obesity, and other risk factors related to metabolic syndrome[68]. An animal study showed that β3-AR activation improved MASLD by regulating fatty acid metabolism, promoting fatty acid oxidation, increasing the activity of stearoyl-CoA desaturase 1, and enhancing triglyceride synthesis. This activation alleviated liver lipid deposition induced by PM 2.5 exposure[69].

Liver regeneration

Time dependent changes of α 1-AR in liver regeneration. An animal study showed that within 2 h after partial liver resection in rats, the content of membrane-bound Ras p21 protein in the liver sharply decreased, which may play a role in the early signal transduction of α 1-AR desensitization. Between 16 and 24 h post-surgery, the coupling of α1-AR with phosphatidylinositol hydrolysis is disrupted, leading to dysregulated intracellular signaling. Between 48 and 72 h post-surgery, the binding capacity of α1-AR decreases, which may be associated with reduced α1-AR-mediated signaling for cell proliferation. In the early stages of liver regeneration, α1-AR promotes hepatocyte proliferation by regulating DNA synthesis and cell cycle progression. However, the aforementioned time-dependent changes may relate to gene expression and cell cycle regulation during the early phases of liver regeneration[53].

The regulatory effect of β 2-AR on liver regeneration (mechanism and experimental verification). Another animal study found that during liver regeneration induced by 70% partial hepatectomy, the expression of β2-AR was significantly upregulated. Further studies showed that the absence of β2-AR led to a mortality rate of up to 62% in mice within 2 days after liver resection, accompanied by a decline in hepatocyte proliferative capacity and impaired liver function. Additionally, β2-AR overexpression mediated by adeno-associated virus (AAV8) significantly promoted liver regeneration. The study also revealed the mechanism by which β2-AR participates in liver regeneration, β2-AR recruits G-protein-coupled receptor kinase 2 to the cell membrane, where it forms a complex with the c-met receptor, activating the downstream ERK

signaling pathway and thereby promoting hepatocyte proliferation. Inhibition of c-met or ERK signaling pathways significantly obstructed the hepatocyte proliferative effects induced by β2-AR overexpression[32].

Liver fibrosis and cirrhosis

Promotion mechanism of receptors on liver fibrosis (HSC activation and collagen deposition). Liver fibrosis is a common disease caused by chronic liver injury, and effective treatments are currently lacking. Activation of α/β-adrenergic receptors (α/β-ARs) activates HSCs through inflammatory factors such as TGF-β and PDGF, leading to HSC activation and promoting collagen deposition[70]. Specifically, α1-AR activation upregulates the expression of TGF-β, while β2-AR activation enhances the ERK signaling pathway, further promoting HSC activation. Ultimately, these processes lead to collagen deposition, triggering liver fibrosis. Antagonists targeting these receptors—such as α1-AR antagonists, which reduce TGF-β upregulation, and β2-AR antagonists, which inhibit ERK pathway activity—can slow HSC activation and collagen deposition, thus decreasing the progression of fibrosis[71]. However, the efficacy of these antagonists in human hepatic fibrosis remains to be validated by large-scale randomized controlled trials (RCTs), and they currently represent merely a potential therapeutic direction. Clinical studies have shown that liver cirrhosis patients treated with long-term β-blockers exhibit a significant increase in intracellular cAMP levels under adrenergic stimulation, suggesting that chronic β-blocker therapy restores β-adrenergic receptor responsiveness to catecholamine stimulation[72].

Improvement effect of α 1-AR antagonist on hepatic sinusoidal capillary metaplasia. One of the most important features of liver fibrosis and cirrhosis is the decreased permeability of liver sinusoidal endothelial cells. Studies have shown that α1-AR antagonists, such as doxazosin, alleviate liver sinusoid capillarization and hepatic angiogenesis by inhibiting the expression of vascular endothelial cell markers (such as CD31 and vWF), thereby alleviating liver fibrosis[18].

Association between receptors and portal hypertension in cirrhosis (treatment strategies and mechanisms)

Application of beta blockers in the treatment of portal hypertension (clinical research evidence). Portal hypertension is a major feature of cirrhosis, which can lead to other serious complications, such as liver cancer, hepatopulmonary syndrome, and hepatorenal syndrome[73]. Currently, β-blockers are the recommended drugs for the treatment of portal hypertension. The latest multicenter RCTs have confirmed that the combined therapy of AR modulators with endoscopy or other drugs exhibits superior efficacy in severe portal hypertension. A study involving 330 patients with Child-Turcotte-Pugh class B/C cirrhosis and high-risk esophageal varices showed that the 1-year first bleeding rate in the group treated with carvedilol (a non-selective β-AR antagonist with α1-AR antagonistic activity) combined with variceal band ligation was significantly lower (6.3%) than that in the carvedilol monotherapy group (20%) and the variceal band ligation monotherapy group (14.5%). Additionally, the hepatic venous pressure gradient (HVPG) was reduced by 25.1%, suggesting that the synergistic blockade of α/β-AR can enhance the control of portal pressure[74]. Furthermore, in patients with an inadequate response to traditional β-AR blockers (HVPG reduction <20%), the combination of carvedilol and simvastatin resulted in a further decrease of HVPG by 2.97 mmHg (compared with 2.05 mmHg in the monotherapy group). Meanwhile, this combination improved endothelial function and reduced the levels of inflammatory factors such as IL-6. These findings indicate that the combination of AR modulators and lipid-lowering drugs can alleviate hepatofibrosis through multiple pathways[75].

Core mechanism of β—receptor blockers in reducing portal hypertension. β-blockers reduce portal hypertension primarily through two mechanisms. First, they block β1-adrenergic receptors in the heart, reducing cardiac output and mean arterial pressure[76]. Second, β-blockers block β2-adrenergic receptors in blood vessels, causing visceral vasoconstriction, which results from the unopposed action of α1-adrenergic receptors[77].

Regulatory effect of β 3-AR on portal hypertension (animal experimental evidence). In experimental portal hypertension in cirrhotic rats, the expression of β3-adrenergic receptors in the liver and portal vein was significantly increased, especially in perivascular regions[34]. Another animal experiment demonstrated that stimulation of β3-AR led to the relaxation of HSCs through cAMP accumulation and inhibition of Rho-kinase activity, reducing hepatic resistance and portal vein pressure in cirrhotic rats[34,49]. These interactions and mechanisms are comprehensively depicted in Fig. 3, which illustrates the molecular pathways driving the progression from a healthy liver to cirrhosis, highlighting the roles of α1-AR, β2-AR, and β3-AR.

Precautions for the use of beta blockers (risk of discontinuation). Nevertheless, β-blocker withdrawal in high-risk cardiovascular patients may trigger rebound hypertension, angina, or infarction, underscoring the need for gradual dose reduction[78].

Liver cancer

Among the various types of primary liver cancer, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC) account for approximately 75%-80%and 10%-15% of cases, respectively[79–81]. A growing body of research indicates that both α-ARs and β-ARs play important roles in the initiation and progression of HCC and ICC.

Hepatocellular carcinoma

Effects of α 2-AR on HCC (angiogenesis, cell behavior, and immune microenvironment). α-ARs play an important role in the initiation and progression of HCC. An in vitro cell experiment study showed that α2-AR is involved in angiogenesis in HCC. The α2-AR agonist DEX can upregulate the expression of HIF-1α and VEGFA in liver cancer cells, promoting angiogenesis in HCC. In a mouse model of liver cancer, DEX also increased tumor microvascular density, further indicating that α2-AR promotes liver cancer angiogenesis via the HIF-1α/VEGFA signaling pathway. Additionally, α2-AR regulates various biological behaviors, such as proliferation, migration, and invasion of liver cancer cells. Meanwhile, the study found that the α2-AR agonist DEX promotes the proliferation and invasion of liver cancer cells, which may be related to its upregulation of HIF-1α/VEGFA expression. HIF-1α regulates the expression of several genes associated with tumor progression, suggesting that α2-AR may play a role in the proliferation and invasion of liver cancer cells through the HIF-1α/VEGFA signaling pathway. Furthermore, α2-AR plays an important role in the immune microenvironment of liver cancer. Studies have found that α2-AR agonists can suppress T cell function in the liver cancer immune microenvironment, which may be associated with their upregulation of HIF-1α expression. HIF-1α promotes the production of immunosuppressive cytokines, suggesting that α2-AR regulates the immune microenvironment through HIF-1α, thereby promoting liver cancer development[82].

Impact of β - AR on HCC (clinical efficacy and mechanism study). **Clinical study: association between β—receptor blockers and prognosis of HCC patients**

β-ARs also play a significant role in the initiation and progression of hepatocellular carcinoma. Clinical studies have shown that liver cancer patients treated with β-adrenergic receptor blockers, especially non-selective β-AR blockers, have a lower liver cancer-specific mortality rate. In patients with HCC complicated by esophageal varices, the efficacy of AR modulators in preventing bleeding should be determined based on tumor staging. A RCT involving 144 HCC patients with medium-to-large esophageal varices showed that the 1-year first bleeding rate of endoscopic variceal ligation was significantly lower (9.7%) than that of propranolol (26.4%). Moreover, in patients with Barcelona Clinic Liver Cancer stage A/B, the endoscopic variceal ligation group had better overall survival (1-year OS: 92% vs. 78%). At the same time, no significant difference was observed in patients with

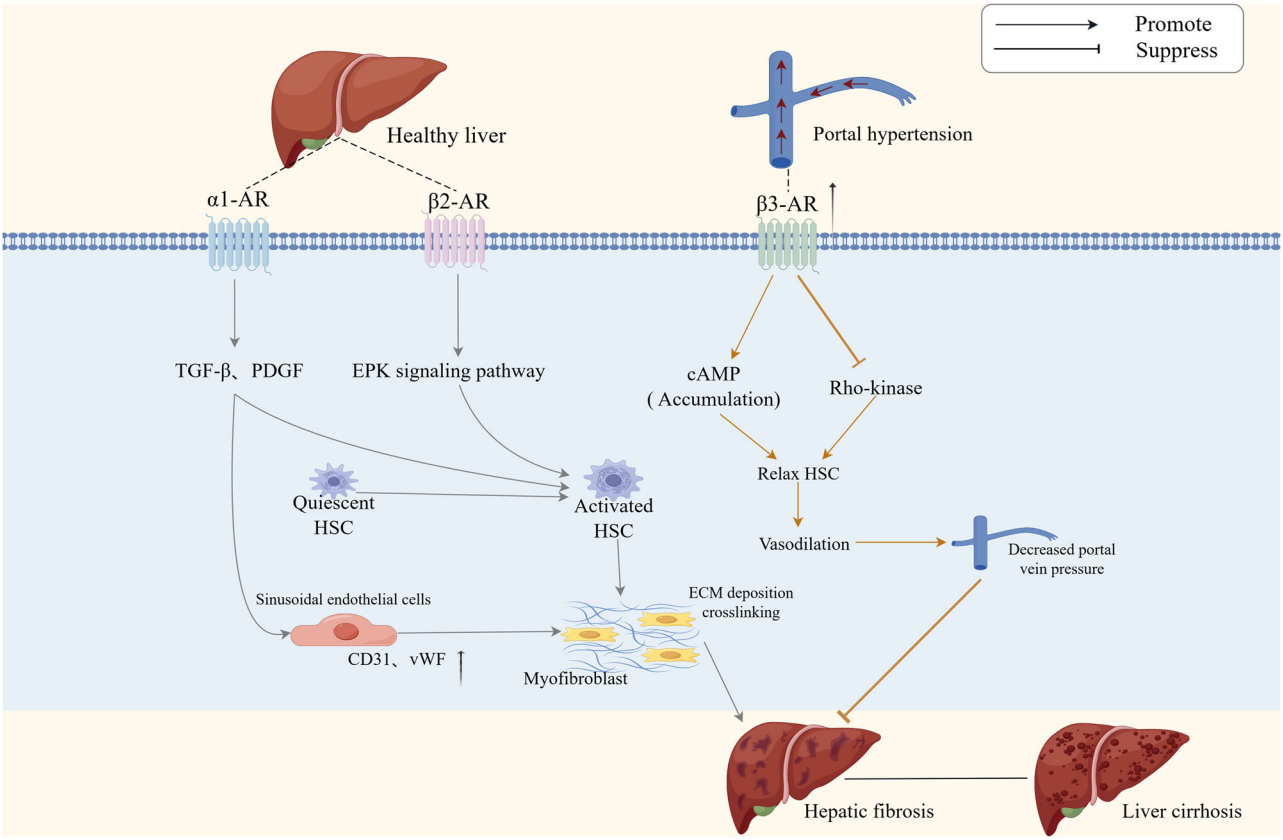

Fig. 3 | Mechanisms of liver fibrosis progression: role of α1-AR, β2-AR, and β3-AR in hepatic fibrosis and cirrhosis (By Figdraw.). This figure depicts the mechanisms by which α1-AR, β2-AR, and β3-AR regulate the progression from a healthy liver to hepatic fibrosis and cirrhosis. In a healthy liver, α1-AR activation upregulates Transforming Growth Factor - β (TGF - β) and Platelet - Derived Growth Factor (PDGF), promoting the transition of HSCs from a quiescent to an activated state. β2-AR activation enhances the ERK signaling pathway, also facilitating HSC activation. Activated HSCs differentiate into myofibroblasts, driving ECM deposition and cross - linking. Additionally, α1-AR promotes the expression of CD31 and vWF in sinusoidal endothelial cells, exacerbating sinusoidal capillarization and fibrosis. In portal hypertension, β3-AR is upregulated. Its activation leads to cAMPaccumulation and inhibition of Rho - kinase, causing HSC relaxation and vasodilation, which decreases portal vein pressure and counteracts portal hypertension and liver cirrhosis progression. Arrows indicate promotion, and blocked lines indicate suppression.

Barcelona Clinic Liver Cancer stage C/D[83]. For advanced HCC patients receiving tyrosine kinase inhibitor therapy, transjugular intrahepatic portosystemic shunt combined with β-AR antagonists could reduce the rebleeding rate (5.8% vs. 25.9%) and improve tyrosine kinase inhibitor adherence (79% vs. 55%), with an 18-month OS rate of 73% (compared with 15% in the endoscopy + β-AR antagonist group). These results suggest that AR modulators need to be combined with interventional therapy to exert a synergistic effect in advanced HCC[84]. This phenomenon may be closely related to β-AR blockers reducing the risk of liver-related decompensated death and promoting early cancer detection[85].

Cell experiment: β—AR regulates the signaling pathway of HCC cell proliferation

In liver cancer cell lines, HepG2 and Huh7, the expression of β-AR is significantly higher than in normal liver cell lines (LO2), with a particularly high expression of β2-AR in HepG2 cells. Norepinephrine (NE) promotes the proliferation of HepG2 cells, and this effect depends on β-AR activation, which can be inhibited by the β-AR antagonist propranolol. NE activates the phosphorylation of ERK1/2 and CREB in HepG2 cells, and this effect can be inhibited by the MEK1/2 inhibitor U0126, indicating that NE promotes HepG2 cell proliferation via the ERK1/2/CREB signaling pathway. Inhibition of CREB activity significantly suppresses the proliferative effect of NE on HepG2 cells[86]. Additionally, in liver cancer cell lines HepG2 and HepG2.2.15, the expression of β-adrenergic receptors (mainly β2 receptors) is significantly higher than in the normal liver cell line HL-7702. The non-selective β-blocker propranolol can inhibit liver cancer cell proliferation, which may be related to the suppression of β2 receptor expression. Propranolol promotes apoptosis in liver cancer cells and induces G1 phase arrest, potentially inducing hepatocyte apoptosis through the caspase-dependent apoptosis signaling pathway. The inhibitory effect of propranolol on the HepG2.2.15 liver cancer cell line is weaker than on HepG2, possibly due to the expression of HBV in HepG2.2.15, with no significant toxicity on the normal liver cell line HL-7702[87].

β 2-AR (ADRB2) regulates HCC progression through autophagy and metabolism

Moreover, adrenaline promotes the development of diethylnitrosamine-induced liver cancer via activation of the β2-adrenergic receptor (ADRB2). ADRB2 is highly expressed in liver cancer cell lines and liver cancer tissues. Activation of ADRB2 promotes liver cancer cell proliferation and survival by inhibiting autophagy. Specifically, ADRB2 activation inhibits the formation of the Beclin1/Vps34/Atg14 complex, thus suppressing autophagy, a process dependent on Akt activation. ADRB2 activation also stabilizes HIF1α by inhibiting autophagy-mediated HIF1α degradation, promoting glucose metabolism in liver cancer cells. The stabilization of HIF1α enhances the expression of glucose transporter proteins and hexokinase. Blocking ADRB2 signaling enhances sorafenib-induced autophagy and improves the antitumor effects of sorafenib, likely because ADRB2 inhibition promotes the degradation of HIF1α. The expression level of ADRB2 is positively correlated with the expression of HIF1α in liver cancer patients, and high ADRB2 expression is closely related to poor prognosis in liver cancer[88].

Intrahepatic cholangiocarcinoma

Expression characteristics of adrenergic receptors in ICC. Compared to non-tumor liver tissue, the density of α1- and β2-adrenergic receptors in

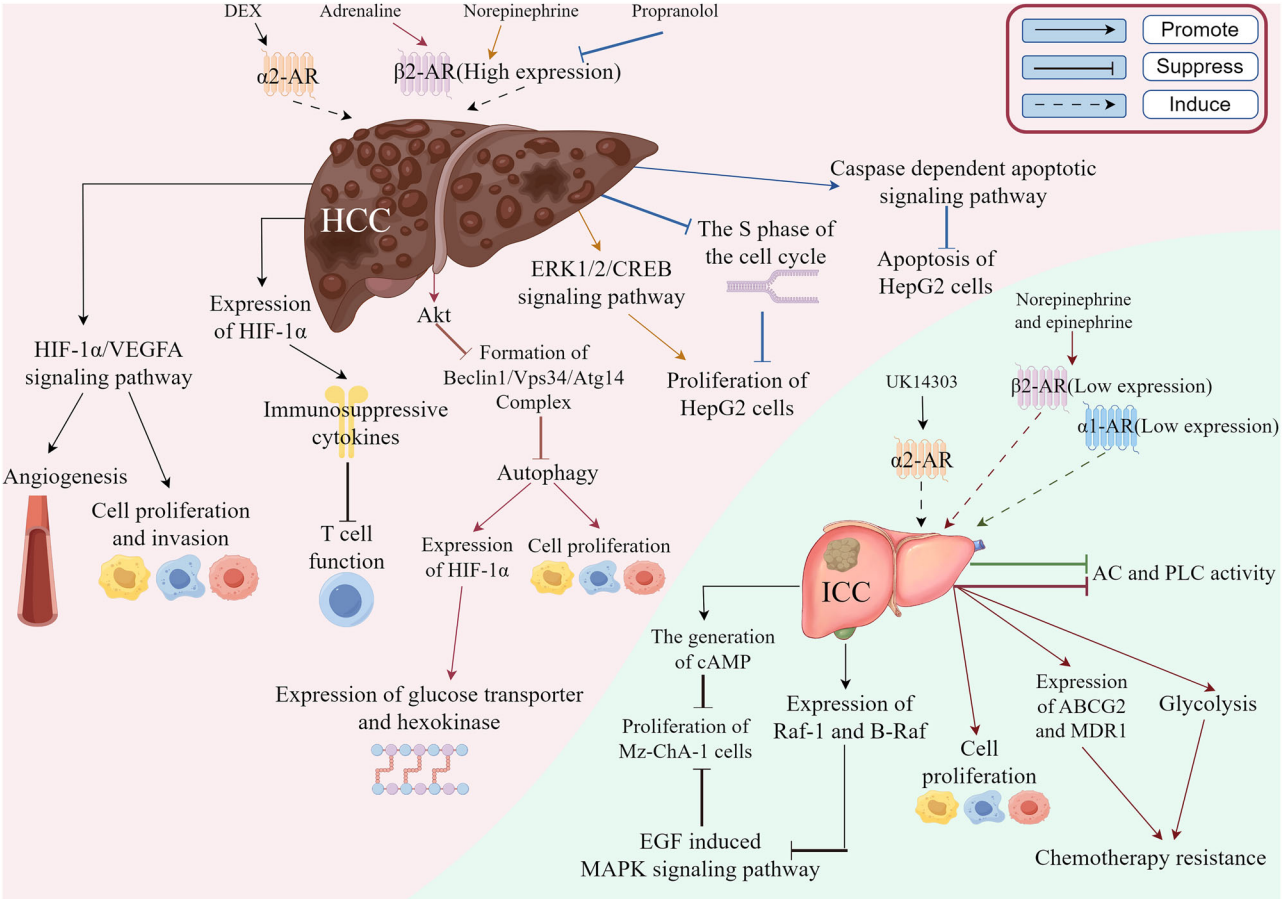

Fig. 4 | Mechanisms of α-AR and β-AR involvement in the progression of HCC and ICC (By Figdraw.). Upper left corner area: This figure shows how α-AR and β-AR regulate HCC and ICC progression. In HCC, α2-AR activation by DEX induces Hypoxia - Inducible Factor - 1α (HIF - 1α) expression, activating the VEGFA pathway to promote angiogenesis, and cell proliferation and invasion. β2-AR (high expression) is activated by adrenaline and norepinephrine; adrenaline activates the Extracellular Signal - Regulated Kinase 1/2/Cyclic Adenosine Monophosphate Response Element - Binding Protein (ERK1/2/CREB) pathway to promote HepG2 cell proliferation, and norepinephrine promotes autophagy via the Akt - Beclin1/Vps34/Atg14 complex pathway, which upregulates HIF - 1α and glucose transporter/hexokinase expression. β2-AR also induces immunosuppressive cytokines to inhibit T - cell function. Propranolol suppresses β2-AR, inducing HepG2 cell apoptosis via the caspase - dependent pathway and blocking the cell cycle's S phase to inhibit proliferation. Bottom right corner area: In ICC, α2-AR activation by UK14303 increases cAMP to inhibit Mz - Cha - 1 cell proliferation and the Epidermal Growth Factor (EGF) - induced Mitogen - Activated Protein Kinase (MAPK) pathway by reducing Raf - 1 and B - Raf expression. Norepinephrine and epinephrine act on low - expressed β2-AR and α1-AR, enhancing AC and PLC activity to promote cell proliferation, upregulate ATP - Binding Cassette Subfamily G Member 2 (ABCG2) and Multidrug Resistance 1 (MDR1) expression to induce chemotherapy resistance, and boost glycolysis. Solid arrows indicate promotion, blocked lines indicate suppression, and dashed arrows indicate inducement.

ICC is significantly reduced. Additionally, the activity of AC and PLC in tumor tissue is also significantly decreased. These changes suggest that the downregulation of adrenergic receptors may be associated with metabolic disorders in intrahepatic cholangiocarcinoma and the regulation of its growth and invasion[89].

Regulation of α 2-AR on ICC cell proliferation and signaling pathway. α-ARs play an important role in ICC, primarily by regulating cell proliferation and the MAPK signaling pathway. An in vitro cell experiment showed that the α2-AR agonist UK14,304 can increase cAMP levels in the cholangiocarcinoma cell line Mz-ChA-1, inhibit cell proliferation and suppress EGF-induced MAPK pathway activity by acutely upregulating Raf-1 and continuously activating B-Raf. This indicates that α2-AR modulates the cAMP signaling pathway and acts downstream of Ras, providing a potential new strategy for the treatment of ICC[90].Fig. 4 illustrates the mechanisms by which α-AR and β-AR contribute to the progression of HCC and ICC, highlighting their roles in tumor proliferation, immune evasion, and chemotherapy resistance.

Association between β 2-AR and ICC chemotherapy resistance. In the treatment resistance of ICC, adrenergic receptors (especially β2-AR) also play a critical role. NE and adrenaline activate the ADRB2, which not only enhances ICC cell proliferation but also interferes with the efficacy of the chemotherapy drug gemcitabine. Furthermore, these activations promote the expression of drug efflux-related genes such as ABCG2 and MDR1, and increase glycolytic activity, thereby conferring resistance to chemotherapy drugs in ICCAA cells. Therefore, inhibiting adrenergic receptors, especially β2-AR, may be an effective strategy to enhance chemotherapy efficacy[91].

Table 1 summarizes the types of adrenergic receptors, their mechanisms of action, and their effects on liver pathophysiology across different liver diseases, helping to understand the crucial role these receptors play in disease progression.

Adrenergic receptors in the treatment of liver diseases

α-adrenergic receptor agonists/antagonists in liver disease treatment

α-adrenergic receptor agonists

Regulatory effect on liver metabolism (Ca^{2+}-related mechanism). The application of α-adrenergic receptor agonists in the treatment of liver diseases is an area of growing research interest. These drugs, by activating α-adrenergic receptors within liver cells, can influence intracellular Ca^{2+} concentrations, thereby regulating liver metabolism. An in vitro cell

Table 1 | The role of adrenergic receptors in liver diseases

Disease/Condition	Adrenergic receptor type	Mechanism of action	Effect on liver pathophysiology	Therapeutic implications	Reference
Liver Inflammation	α1-AR, β-AR	α1-AR: PLC-IP3/DAG-PKC/PKD signaling pathway, β-AR: IL-6 secretion	Increases inflammation and modulates drug metabolism	β-AR antagonists to reduce inflammation and drug interaction risks	52–54
Liver Injury	α2-AR, β-AR	α2-AR: activates GSK-3β/MKP-1/Nrf2, β-AR: exacerbates hepatotoxicity	Modulates oxidative stress and apoptosis exacerbates liver injury	α2-AR agonists to protect against oxidative stress	57,58
steatotic Liver (ALD, MASLD)	α1-AR, α2-AR, β1-AR, β2-AR, β3-AR	β2-AR: increases lipid synthesis, β3-AR: promotes fatty acid oxidation	Accelerates fat accumulation, fibrosis, and lipid metabolism	β2-AR antagonists and β3-AR agonists to regulate lipid metabolism	37,66,67,69,117
Liver Regeneration	α1-AR, β2-AR	α1-AR: regulates cell proliferation, β2-AR: ERK signaling pathway	Facilitates hepatocyte proliferation and regeneration	β2-AR agonists to promote liver regeneration	32,53
Liver Fibrosis & Cirrhosis	α1-AR, β2-AR, β3-AR	α1-AR: TGF-β upregulation, β2-AR: ERK pathway activation	Promotes HSC activation, collagen deposition, and fibrosis	α1-AR antagonists for fibrosis treatment, β-AR antagonists for portal hypertension	70,71,76,77
Liver Cancer (HCC & ICC)	α2-AR, β2-AR	α2-AR: HIF-1α/VEGFA signaling pathway, β2-AR: ERK/CREB signaling pathway	Promotes cancer cell proliferation, invasion, and immune evasion	β-AR antagonists to reduce mortality	82,86,87

The table mainly presents the mechanisms of action of various types of adrenergic receptors in multiple liver diseases, their impacts on liver pathophysiology, and their corresponding therapeutic significance. It provides crucial information for understanding the pathogenesis of liver diseases and potential therapeutic strategies.

experiment showed that phenylephrine, by stimulating α-adrenergic receptors, increases intracellular Ca^{2+} levels, thereby promoting metabolic processes such as glycogenolysis and gluconeogenesis. However, the mechanism of action of α-adrenergic receptor agonists is complex. An animal experiment found that α-adrenergic receptor agonists not only promote the release of Ca^{2+} but also inhibit the liver's release of Ca^{2+}, and this effect can be inhibited by pertussis toxin. Additionally, these drugs can affect liver vascular function and the liver cells' sensitivity to other hormones.

Effects of ethanol exposure on receptor function. It is worth noting that ethanol exposure alters the interaction between α-adrenergic receptors and Ca^{2+}-ATPase. Chronic ethanol exposure leads to an increase in Ca^{2+}-ATPase activity and in the presence of phenylephrine, the enzyme activity is further enhanced. This suggests that ethanol alters the interaction between α-adrenergic receptors and Ca^{2+}-ATPase, thereby reducing the receptor's ability to regulate intracellular Ca^{2+} levels. These changes may impact the liver's ability to maintain Ca^{2+} levels for second messenger functions such as glycolysis and gluconeogenesis[92,93].

Signal transduction related mechanisms (association between G protein and phospholipase C). In terms of signal transduction, the effects of α-adrenergic receptor agonists are likely closely related to post-receptor signaling pathways. An animal study has shown that pertussis toxin can inhibit certain effects of α-adrenergic receptors, suggesting the presence of signaling pathways associated with α-adrenergic receptors that are inhibited by pertussis toxin[26]. Furthermore, α-adrenergic receptors play a crucial role in various cellular processes, such as activating phospholipase C on the membrane of rat hepatocytes. α-Adrenergic receptor agonists can stimulate phosphoinositide metabolism and cause the accumulation of inositol trisphosphate. Another animal study also confirmed the interaction between pertussis toxin-sensitive guanine nucleotide-binding regulatory proteins (G-proteins) and α-adrenergic receptors[94].

α-adrenergic receptor antagonists

Therapeutic effect on liver fibrosis and cirrhosis. **Animal experimental evidence (carbon tetrachloride induced model)**

Liver fibrosis and cirrhosis are complex clinical conditions caused by chronic liver injury, and effective treatments are currently lacking, making this field a critical area of research. In a mouse model of liver fibrosis induced by carbon tetrachloride (CCl_4), researchers found that treatment with the α-adrenergic receptor antagonist doxazosin significantly alleviated the degree of liver fibrosis and reduced hepatic capillarization. Furthermore, doxazosin inhibited angiogenesis in human umbilical vein endothelial cells and human hepatic sinusoidal endothelial cells. These findings suggest that doxazosin exerts therapeutic effects on liver fibrosis by reducing liver sinusoidal capillarization and hepatic angiogenesis[18].

Mechanism deepening (histological and cellular level)

Further animal studies have shown that doxazosin effectively alleviated CCl_4-induced liver fibrosis in mice. Histological staining results showed that doxazosin reduced CCl_4-induced collagen deposition and inflammatory cell infiltration in the liver while improving intrahepatic angiogenesis and portal venous pressure. Scanning electron microscopy observations revealed that doxazosin increased the number of fenestrae in liver sinusoidal cells and reduced the expression of endothelial cell markers CD31 and vWF, indicating that doxazosin can regulate the process of sinusoidal capillarization, thus alleviating liver fibrosis. Additionally, doxazosin inhibited the proliferation of human hepatic sinusoidal endothelial cells and umbilical vein endothelial cells induced by vascular endothelial growth factor (VEGF), further confirming its anti-angiogenic effect and ability to mitigate liver fibrosis[18].

Regulation of autophagy and apoptosis in hepatic stellate cells (HSC). Autophagy and apoptosis are two crucial catabolic pathways for maintaining biological homeostasis, especially in the liver, where dysregulation of these processes can lead to liver fibrosis[95]. An in vitro cell experiment

showed that carvedilol can alleviate fibrosis by inhibiting autophagy and inducing apoptosis in HSCs, further supporting the idea that α-adrenergic receptor antagonists can inhibit the onset and progression of liver fibrosis[96].

Protective effect on drug-induced liver injury (acetaminophen induced). α1-adrenergic receptor antagonists may confer substantial protection against acetaminophen-induced hepatotoxicity; this putative protective effect appears to be associated with the absence or marked reduction of red blood cell accumulation in the liver, although a causal relationship cannot be established from the available data. On one hand, elevated catecholamine levels may contribute to liver injury and acetaminophen-induced hepatotoxicity by impairing liver perfusion.

Application in the treatment of liver cirrhosis combined with esophageal varices (clinical research evidence). The long-term benefits of α/β-AR dual antagonists (e.g., carvedilol) in liver cirrhosis have been confirmed by RCTs. An RCT with a maximum follow-up duration of 20 years showed that the median overall survival in the carvedilol group (7.8 years) was significantly better than that in the endoscopic variceal ligation group (4.2 years). Additionally, the risk of non-liver-related mortality (such as from cardiovascular events) was reduced by 35%. These findings suggest that the efficacy of carvedilol may go beyond simple portal pressure control and involve multi-organ protection[97]. Furthermore, in patients with HBV-related compensated liver cirrhosis and medium-sized esophageal varices, the combination of carvedilol and nucleoside analogs achieved a variceal regression rate of 43.5%, compared with 13.1% in the nucleoside analogs monotherapy group. However, it showed no significant effect on small esophageal varices, indicating that the efficacy of AR antagonists is associated with the grading of esophageal varices[98]. On the other hand, Prazosin toxicity is associated with a significant accumulation of red blood cells in the hepatic sinusoids, and doxazosin completely prevents this accumulation. These findings highlight the potential clinical significance of α1-adrenergic antagonists in managing acetaminophen overdose and acute liver failure in patients[99]. However, their protective efficacy against acetaminophen-induced acute liver failure in humans remains unsubstantiated, and such agents cannot be deemed equivalent to "complete protection". Thus, further clinical investigations are warranted to assess their true therapeutic value.

Relieve effect on liver inflammation. An animal study also reveal the crucial role of α-adrenergic receptors in liver inflammation. α1-adrenergic receptor agonists promote the release of inflammatory cytokines from hepatocytes, while α1-adrenergic receptor antagonists can alleviate hepatic inflammation. Based on this discovery, α1-adrenergic receptor antagonists hold the potential for treating inflammatory liver diseases, such as viral hepatitis and autoimmune liver diseases[18].

Potential value in the treatment of liver cancer (basic research stage). Additionally, α-adrenergic receptor antagonists show promise in liver tumor treatment. In xenograft models of HCC in animals, α1-adrenergic receptor (α1-AR) antagonists have been shown to exert inhibitory effects on tumor cell proliferation and metastasis. Notably, however, clinical trials investigating the safety and efficacy of these antagonists in human HCC remain uninitiated. At present, α1-AR merely represents a potential therapeutic target confined to the realm of basic research, and further translational validation is indispensable to corroborate its relevance for clinical application[18,100].

These diverse roles of α-AR agonists and antagonists in regulating liver toxicity, fibrosis, inflammation, and tumor progression are illustrated in Fig. 5, highlighting their broad therapeutic potential in liver diseases.

Safety considerations for α-adrenergic receptor modulators. While α-adrenergic antagonists show promise in treating liver fibrosis and inflammation, their systemic effects warrant caution. Notably, α-blockers (e.g., doxazosin, tamsulosin) may induce orthostatic hypotension, dizziness, and intraoperative floppy iris syndrome (IFIS) during cataract surgery due to iris smooth muscle relaxation[101]. In patients with pheochromocytoma, α-blockers are essential for preoperative blood pressure control but require careful titration to avoid paradoxical hypertension or arrhythmias[102]. Extrahepatic monitoring is advised, particularly in elderly patients or those with cardiovascular comorbidities.

β-adrenergic receptor agonists/antagonists in the treatment of liver diseases

β-adrenergic receptor agonists

Regulatory effect on bile duct remodeling (evidence from chronic liver injury model). An animal study found that activation of β-adrenergic receptors can promote bile duct dilatation caused by chronic liver injury, further confirming the regulatory role of hepatic sympathetic nerves in bile duct remodel[48].

Improvement effect of novel agonist ATR-127 on metabolism and fatty liver disease. Another animal model study used the novel ATR-127, targeting skeletal muscle and brown adipose tissue, to address diabetes and steatohepatitis. The study evaluated the effects of ATR-127 in activating β2- and β3-adrenergic receptors. First, the impact of ATR-127 on cAMP accumulation was compared with isoproterenol, and its effects on GLUT4-mediated glucose uptake and cAMP accumulation were investigated in L6 muscle cells. Although ATR-127 showed lower cAMP accumulation in L6 muscle cells, it significantly enhanced GLUT4-mediated glucose uptake. Further in vitro and in vivo experiments demonstrated that ATR-127 significantly increased glucose uptake and thermogenesis in brown adipose tissue. Treatment with ATR-127 in diet-induced mice with obesity showed that ATR-127 effectively improved glucose homeostasis, reduced body weight and fat mass, enhanced skeletal muscle glucose uptake, increased brown adipose tissue thermogenesis, and improved hepatic steatosis[55].

Therapeutic effect of β 3-AR agonist BRL37344 on MASLD. **Efficacy and mechanism of MASLD rats (lipid metabolism and inflammation regulation)**

The β3-AR agonist BRL37344 significantly improved liver steatosis and inflammation in a rat model of MASLD by modulating lipid metabolism and inflammatory responses. First, β3-AR expression was upregulated, with a significant increase in β3-AR protein and mRNA expression in the liver of MASLD rats induced by an HFD, suggesting that upregulation of β3-AR may serve as a protective mechanism against MASLD. After 4 weeks of BRL37344 treatment, there was a significant reduction in serum ALT, AST, TG, TC, LDL-C, and FFA levels, as well as a decrease in hepatic fat accumulation and inflammation. Histopathological analysis showed that BRL37344 improved liver steatosis, ballooning degeneration, and inflammation.

The impact of gene polymorphism on treatment efficacy (based on precision therapy)

The efficacy of β3-AR is influenced by genetic polymorphism, and personalized intervention is particularly necessary in patients with MASLD. An RCT involving 171 MASLD patients showed that patients carrying the β3-AR Trp64Arg mutation (rs4994) achieved a body weight reduction of 3.2 kg after receiving a "diet guided by nutrient-induced insulin output ratio", compared with 1.1 kg in those on a conventional diet; meanwhile, their homeostatic model assessment of insulin resistance decreased by 28%. These findings suggest that the β3-AR genotype can serve as a biomarker for precision treatment of MASLD[103].

Protective effect on mitochondrial function

Furthermore, BRL37344 improved MASLD by modulating the expression of lipid metabolism-related proteins. Specifically, BRL37344 upregulated the expression of PPAR-α and mCPT-1 while downregulating PPAR-γ and FAT/CD36, thereby reducing lipid accumulation in the liver and promoting β-oxidation of fatty acids. Activation of β3-AR also reduced liver inflammation by modulating the expression of PPARs/mCPT-1 and FAT/CD36, further protecting the liver from MASLD-induced damage. Finally, BRL37344 reversed HFD-induced mitochondrial ultrastructural

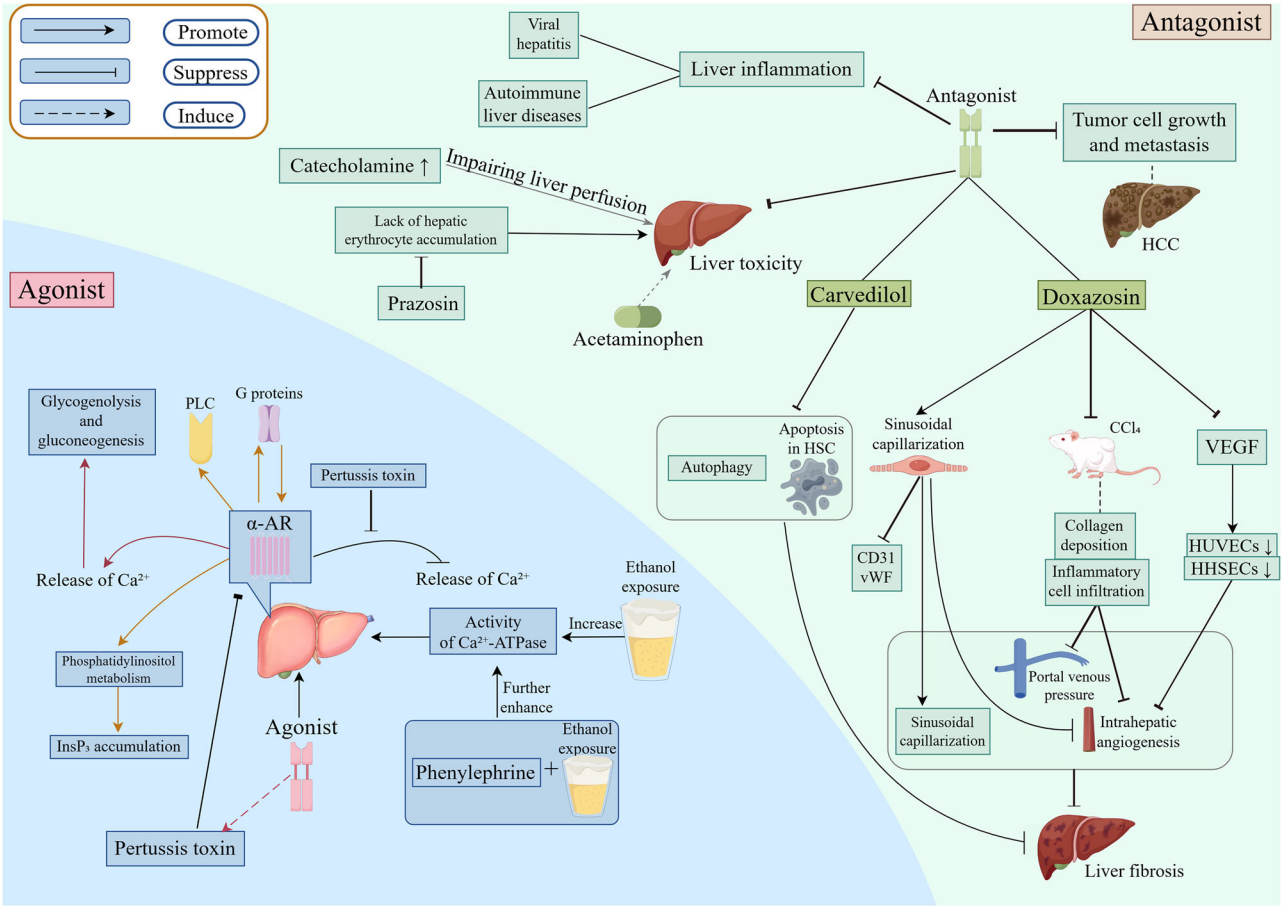

Fig. 5 | Effects of α-AR agonists and antagonists on liver function (By Figdraw.). For agonists: α - AR activation by agonists (like phenylephrine) triggers G proteins and PLC, leading to intracellular Ca^{2+} release, which promotes glycogenolysis, gluconeogenesis, phosphatidylinositol metabolism, and Inositol Trisphosphate ($InsP_3$) accumulation. Ethanol exposure enhances Ca^{2+} - ATPase activity, further amplifying Ca^{2+} - related effects, while Pertussis toxin inhibits G protein - mediated α - AR signaling. For antagonists: Prazosin addresses impaired liver perfusion from elevated Catecholamine and lack of hepatic erythrocyte accumulation. Carvedilol mitigates liver inflammation (from viral hepatitis, autoimmune liver diseases) and liver toxicity (from acetaminophen), and induces HSC apoptosis and autophagy. Doxazosin, in a CCl_4 - induced liver fibrosis mouse model, reduces collagen deposition, inflammatory cell infiltration, sinusoidal capillarization (via CD31 and vWF), portal venous pressure, and intrahepatic angiogenesis (by decreasing VEGF - mediated Human Umbilical Vein Endothelial Cells (HUVECs) and Human Hepatic Sinusoidal Endothelial Cells (HHSECs) activity), thus alleviating liver fibrosis. Also, α - AR antagonists suppress HCC tumor cell growth and metastasis. Solid arrows indicate promotion, blocked lines indicate suppression, and dashed arrows indicate inducement.

damage, reduced mitochondrial swelling and lysosomal increase, suggesting that β3-AR activation may alleviate the progression of MASLD by protecting mitochondrial function[36].

Auxiliary value of β—receptor antagonists in the treatment of secondary fatty liver. In addition, propranolol can reduce the peripheral lipolysis rate (with a 32% decrease in Ra FFA) in burn patients complicated with fatty liver, while maintaining the hepatic very low-density lipoprotein-triglyceride secretion rate to prevent fat accumulation in hepatocytes. This provides a new direction for the treatment of secondary fatty liver with β-AR antagonists[104].

β-adrenergic receptor antagonists

Improving the prognosis of liver cancer (clinical research evidence). Studies have shown that β-adrenergic receptor antagonists have potential therapeutic applications in liver diseases. Clinical studies indicate that the use of non-selective β-receptor antagonists during cancer diagnosis is associated with a lower liver cancer mortality rate, especially with lipophilic β-receptor antagonists. This association is more pronounced in patients without known distant metastases. Individual β-receptor antagonists, such as propranolol and carvedilol, are also linked to lower mortality rates[85].

As summarized in Fig. 6, both β-AR agonists (e.g., improving metabolic dysfunction in MASLD) and antagonists (e.g., reducing liver cancer mortality and modulating inflammation in cirrhosis) demonstrate multifaceted roles in liver disease progression and treatment.

Regulation of hepatitis and fibrosis (experimental cirrhosis model). The use of β1-adrenergic receptor-selective antagonists in experimental liver cirrhosis has been shown to inhibit norepinephrine-mediated downregulation of TNF-α, suggesting that β-adrenergic receptors may play a role in liver inflammation and fibrosis.

Combination with other drugs enhances the control effect of portal hypertension. The combination of β-AR antagonists with drugs targeting other pathways can enhance the efficacy of portal pressure control. An RCT involving 60 patients with liver cirrhosis showed that the combination of 5-methyltetrahydrofolate and propranolol achieved a 20% reduction in HVPG, compared with a 12.5% reduction in the propranolol monotherapy group. Meanwhile, this combination increased the bioavailability of nitric oxide (with a 110% rise in tetrahydrobiopterin (BH4) levels). The mechanism may be related to 5-methyltetrahydrofolate improving the coupling of endothelial nitric oxide synthase[105].

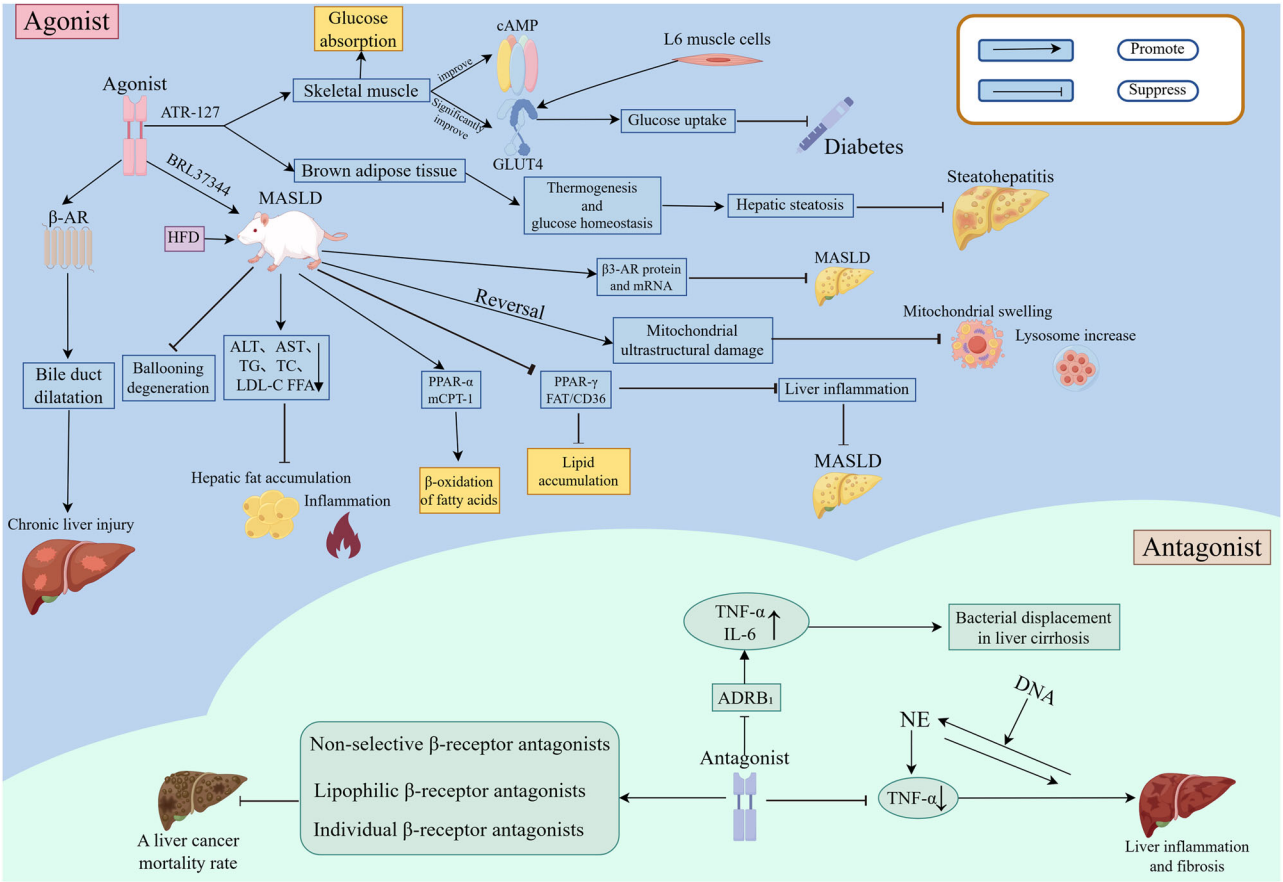

Fig. 6 | Multifaceted effects of β-AR agonists and antagonists in liver disease progression and treatment (By Figdraw.). This figure illustrates the effects of β - AR agonists and antagonists on liver disease. For agonists: ATR-127 activates β - AR in skeletal muscle, enhancing glucose uptake via Glucose Transporter 4 (GLUT4) to improve diabetes, and in brown adipose tissue, regulating thermogenesis and glucose homeostasis to alleviate hepatic steatosis and steatohepatitis. BRL37344 (a β3-AR agonist) in a Mouse fed a High - Fat Diet (HFD, inducing MASLD) reduces serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Triglyceride (TG), Total Cholesterol (TC), Low - Density Lipoprotein Cholesterol (LDL - C), and Free Fatty Acid (FFA) levels, mitigates hepatic fat accumulation, inflammation, ballooning degeneration, and bile duct dilation, reverses β3-AR protein and mRNA reduction, alleviates mitochondrial ultrastructural damage (less swelling and fewer lysosomes), and regulates Peroxisome Proliferator - Activated Receptor α (PPAR - α, promoting fatty acid β - oxidation via mitochondrial Carnitine Palmitoyltransferase 1, mCPT - 1) and PPAR - γ (promoting lipid accumulation via Fatty Acid Translocase/Cluster of Differentiation 36, FAT/CD36) to impact liver inflammation and MASLD. For antagonists: Non - selective, lipophilic, and individual β - receptor antagonists are linked to reduced liver cancer mortality. Antagonizing Adrenoceptor Beta 1 (ADRB1) inhibits Norepinephrine (NE) - mediated Tumor Necrosis Factor - α (TNF-α) upregulation, lessens Interleukin - 6 (IL-6) release, and suppresses bacterial DNA - related inflammation in liver cirrhosis, aiding in controlling cirrhosis progression and fibrosis. Solid arrows indicate promotion, and blocked lines indicate suppression.

Delayed effect on the progression of esophageal varices (early intervention value). In addition, carvedilol can delay the progression from small esophageal varices to large ones in patients with small varices (20.8 months vs. 18.7 months). Particularly in patients with MASLD-related liver cirrhosis, HVPG was reduced by 8.64%, suggesting that β-AR antagonists can be used for early intervention in the progression of fatty liver to cirrhosis[106].

Regulation of bacterial translocation in liver cirrhosis (ADRB1 targeting significance). Further research has demonstrated that during liver injury, an interaction occurs between norepinephrine in the liver and inflammation, which is exacerbated by the presence of bacterial DNA. Selective antagonism of ADRB1 leads to an increase in TNF-α and IL-6 levels in the liver, indicating that ADRB1 plays a key role in the pro-inflammatory response that regulates bacterial translocation in cirrhosis. Therefore, targeting ADRB1 may have potential therapeutic significance in preventing bacterial translocation in cirrhosis[85].

Safety considerations for β-adrenergic receptor modulators. β-Blockers remain cornerstone therapies for portal hypertension and cardiac protection in cirrhosis; however, abrupt discontinuation post-myocardial infarction increases mortality by 16%[78]. Non-selective β-blockers (e.g., propranolol, carvedilol) may exacerbate bronchospasm in asthma/COPD, mask hypoglycemia symptoms in diabetics, and cause fatigue due to central nervous system penetration[107,108]. Conversely, β-agonists like mirabegron (for MASLD) can elevate heart rate and blood pressure, necessitating cardiovascular monitoring. Drug selection should balance hepatic benefits against extrahepatic risks, especially in polypharmacy scenarios.

Combined use of α- and β-adrenergic receptor drugs in the treatment of liver diseases

Interaction characteristics of α - AR and β - AR in the liver (synergy and antagonism)

Synergistic effect: promotion of liver pathological process. In certain physiological conditions of the liver, α-AR and β-AR can act synergistically through different signaling pathways, promoting inflammation, liver injury, and the progression of liver fibrosis. Therapeutic strategies targeting these pathways are exemplified by novel drug applications summarized in Table 2, which elaborates mechanisms of

Table 2 | New applications of α- and β-adrenergic receptors in treatment

Treatment category	Adrenergic receptor type	Mechanism of action	Effect on liver pathophysiology	Therapeutic implications	Reference
α-Adrenergic Receptor Agonists	α1-AR, α2-AR	Activation of α-AR increases intracellular Ca^{2+}, regulates liver metabolism, and affects vascular function	Modulates glycolysis, and gluconeogenesis, and influences liver sensitivity to other hormones	Phenylephrine promotes the liver's metabolic processes	92
α-Adrenergic Receptor Antagonists	α1-AR, α2-AR	Antagonism of α-AR reduces fibrosis, capillarization, and angiogenesis in liver tissue	Reduces collagen deposition and liver inflammation, alleviates fibrosis and liver injury	Doxazosin and carvedilol reduce fibrosis, improve blood flow, and protect against acetaminophen-induced liver toxicity	18,99
β-Adrenergic Receptor Agonists	β2-AR, β3-AR	Activation of β-AR promotes glucose uptake, thermogenesis, and liver steatosis reduction	Improves lipid metabolism, reduces liver fat accumulation, and decreases liver inflammation	ATR-127 improves glucose homeostasis and steatotic liver, BRL37344 improves MASLD, protects mitochondrial function	36,55
β-Adrenergic Receptor Antagonists	β1-AR, β2-AR	Blockade of β-AR reduces inflammation and tumor cell growth	Reduces liver inflammation, and fibrosis, and lowers cancer mortality	Propranolol and carvedilol improve survival rates in liver cancer, reduce inflammation, and prevent bacterial translocation in cirrhosis	85
Combined Use of α- and β-Adrenergic Receptor Drugs in the Treatment of Liver Diseases	α1-AR, β1-AR, β2-AR	Combined antagonism of α-AR and β-AR modulates vascular regulation, reduces fibrosis, and improves liver hemodynamics.	Slows fibrosis progression, improves liver function, and alleviates complications from cirrhosis	Prazosin and propranolol together inhibit HSC proliferation, improving liver fibrosis treatment; combined α-AR agonists methoxamine and β-AR antagonists propranolol are significantly effective in portal hypertension and cirrhosis.	7,70,71,77,109

This table elaborates in detail the new applications of α-AR and β-AR, related drugs in the treatment of liver diseases, covering the mechanisms of action of different types of drugs, their impacts on the liver's pathophysiology, and their specific therapeutic significance. It provides multiple drug intervention ideas for the treatment of liver diseases.

action, impacts on liver pathophysiology, and therapeutic significance of α-AR and β-AR modulators.

Antagonistic effect: balanced regulation of vascular function. In other physiological contexts, however, α-AR and β-AR exhibit antagonistic effects, counteracting each other's actions. Particularly in vascular regulation, activation of α1-AR causes vasoconstriction and increases blood pressure, while activation of β2-AR induces vasodilation and lowers blood pressure[5,109–111]. The antagonistic effects between the two receptors help maintain a balance between vasoconstriction and vasodilation.

Advantages and mechanisms of combined use of α-AR and β-AR antagonists

Improvement of liver fibrosis and cirrhotic complications. The combined use of α-AR and β-AR antagonists offers multiple benefits. An animal study has shown that the combined use of α1-AR and β-AR antagonists can slow the progression of liver fibrosis, particularly by reducing the activity of TGF-β to decrease collagen accumulation, lowering portal vein pressure, improving liver hemodynamics, and alleviating complications associated with cirrhosis[71].

Regulation of hepatic stellate cell (HSC) function. Additionally, HSCs, the key cells of the liver, can express adrenergic receptors, and catecholamine biosynthetic enzymes, release NE, and proliferate under the influence of α- and β-adrenergic receptor antagonists. These cells also produce neurotransmitters that respond to the SNS, promoting liver fibrosis.

Clinical research evidence of combination therapy (efficacy in different patient populations)

Dual antagonist vs single β - AR antagonist. The efficacy of combined α/β-AR modulators varies across different populations of patients with liver cirrhosis. A RCT involving 220 patients with liver cirrhosis showed that the 3-year bleeding rate in the carvedilol group (a dual α1/β-AR antagonist) was significantly lower (37.14%) than that in the propranolol group (a single β-AR antagonist, 59.04%). Particularly in patients with large esophageal varices, carvedilol reduced the bleeding risk by 48%, suggesting that the α1-AR antagonistic effect can further enhance the efficacy of β-AR blockers[112].

Metabolomics perspective: biomarkers for monitoring the efficacy of combination therapy. In addition, in patients with compensated liver cirrhosis and clinically significant portal hypertension, metabolomic analysis revealed that the level of "ceramide (d18:1/22:0) + methionine" decreased after carvedilol treatment, which improved the C-index for prognosis prediction (0.808 vs. 0.748). This provides a new biomarker for monitoring the efficacy of combined therapy[113].

Synergistic inhibitory effect of combination therapy on HSC proliferation. Another clinical study showed that the α-AR antagonist prazosin and the β-AR antagonist propranolol individually inhibited HSC proliferation, but their combination led to a more pronounced inhibitory effect, suggesting a synergistic action in suppressing HSC proliferation[70]. This demonstrates that the combined antagonism of α-AR and β-AR could serve as an effective strategy for the treatment of liver fibrosis and cirrhosis and warrants further investigation.

Exploration of new combination therapy regimens (multicenter clinical trials)

Combination of carvedilol and simvastatin: for patients with poor response to traditional beta blockers. Recent clinical trials explore synergistic approaches targeting both α and β-ARs. A multicenter randomized trial[75] demonstrated that carvedilol (non-selective β-blocker with anti-α1 activity) combined with simvastatin enhanced portal pressure reduction in cirrhosis patients with suboptimal response to traditional β-blockers. This combination reduced HVPG by 18.9% versus 12.5% with carvedilol alone, attenuated postprandial endothelial dysfunction, and decreased proinflammatory cytokines (IL-6, MCP-1).

Midodrine (alpha 1 agonist) combined with propranolol: for patients with refractory ascites. Similarly, Ranjan et al. [114] reported that midodrine (α1-agonist) added to propranolol allowed higher β-blocker dosing, achieving greater HVPG reduction (23.5% vs. 14.5%) and significantly lowering first-bleed risk in refractory ascites patients.

Methoxymine (alpha agonist) combined with propranolol: regulation of portal hypertension hemodynamics. A separate study involving 26 patients with portal hypertension and cirrhosis showed that the α-agonist methoxamine and the β-blocker propranolol reduced liver blood flow and splenic vein blood flow through different mechanisms, respectively[77]. This suggests that while they have distinct mechanisms of action in treating portal hypertension, their combined use can alleviate the symptoms of portal hypertension.

Future directions: clinical trials and emerging therapies

Clinical trial focus on β—AR (synergistic combination and novel agonists). Ongoing clinical trials prioritize receptor-specific modulation to enhance therapeutic efficacy while minimizing systemic adverse effects. For β-adrenergic receptors (β-ARs), recent trials focus on synergistic combinations and novel agonists. A multicenter randomized study demonstrated that carvedilol (a non-selective β-blocker with intrinsic anti-α1 activity) combined with simvastatin reduced HVPG by 18.9% versus 12.5% with carvedilol alone in cirrhosis patients with suboptimal response to traditional β-blockers, concurrently attenuating postprandial endothelial dysfunction and proinflammatory cytokines (IL-6, MCP-1)[75]. Novel β3-AR agonists (e.g., BRL37344) in MASLD models reversed hepatic steatosis via PPARα/mCPT-1 pathways, improving mitochondrial function and reducing lipid accumulation[87]. Dual β2/β3-agonists like ATR-127 enhanced glucose uptake in skeletal muscle and brown adipose tissue, reduced hepatic inflammation, and ameliorated steatosis in diet-induced obesity[55]. Additionally, β-blocker withdrawal protocols are under investigation to mitigate rebound hypertension in patients with cardiovascular comorbidities[78].

Clinical trial focus on alpha AR (hemodynamic optimization). For α-adrenergic receptors (α-ARs), trials explore hemodynamic optimization in advanced cirrhosis. Midodrine (an α1-agonist) added to propranolol enabled higher β-blocker dosing, achieving HVPG reduction of 23.5% versus 14.5% with propranolol alone and significantly lowering first-bleed risk in refractory ascites (Ranjan et al., Hepatol Int 2024). In acute-on-chronic liver failure (ACLF), midodrine titrated to increase mean arterial pressure by ≥8.5 mmHg reduced HVPG, highlighting its role in critical portal hypertension management[115].

Emerging therapies: gene therapy targeting ADRB2. Emerging gene therapies targeting ADRB2 splicing show promise in suppressing hepatocellular carcinoma metastasis by inhibiting autophagy-mediated HIF1α stabilization[116].

Conclusion

In summary, adrenergic receptors play a pivotal role in liver physiology and pathology, holding significant promise as novel therapeutic targets for liver diseases. Although research in this field is still in its early stages, further investigation into the specific mechanisms by which these receptors function in the liver is crucial for advancing our understanding of their involvement in liver disease onset and progression. This deeper knowledge will not only aid in optimizing drug development but also in refining adrenergic receptor agonists and antagonists for enhanced therapeutic efficacy. Future therapeutic strategies must rigorously evaluate extrahepatic safety, particularly cardiovascular and metabolic sequelae of chronic adrenergic modulation.

Moreover, the broader therapeutic potential of adrenergic receptors extends beyond hepatology, with implications for cardiovascular and neurological disorders. Exploring these receptors across multiple disciplines may reveal new avenues for treatment and therapeutic innovation.

As research continues, the application of adrenergic receptors in clinical practice, particularly in hepatobiliary surgery, is poised to drive significant breakthroughs in the treatment of liver and related diseases. Ultimately, these advancements hold the potential to improve patient outcomes and contribute to the development of personalized, precision medicine strategies.

Data availability

All data supporting the findings of this review are included within the manuscript and cited references. No new datasets were generated or analyzed during this study.

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Conceptualization, Y.Y., R.X., M.H.; Methodology, Y.Y., R.X., M.H.; Resources, Y.Y., R.X., M.H.; Supervision, M.H., R.X., Y.Y.; Writing—Original Draft Preparation, Y.Y., Y.H., L.Y., Y.F., Z.G., Y.W., Y.X., J.X.; Writing—Review & Editing, Y.Y., Y.H., L.Y., Y.F., Z.G., Y.W., Y.X., J.X.; Validation, Y.H., Y.F., L.Y.; Visualization, Y.H., Y.F.; Funding Acquisition, M.H., Y.H., Y.F., and L.Y. contributed equally to this work and are co-second authors.

Competing interests

The authors declare no competing interests.

Additional information

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